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A STUDY OF THE MUNITIONS INTOXICATIONS IN FRANCE.

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[EDITORIAL NOTE.—This study was made under the auspices of the National Research Council and represents a great deal of time and effort on the part of the investigators.]

The discovery that many of the various explosives manufactured in Europe and the United States had more or less toxic effects on the workmen who handled them, with many fatal results, has led to a series of studies in the various countries, and to the appointment of various commissions and committees on munitions intoxications. The present attempt at analysis of the question in France was made at the request of the American committee and was carried on while the writer was Medical Associate to the Scientific Attaché at Paris, under the American National Council of Research. The unexpected arrival of the end of the war, with the consequent immediate cessation of activities, made the work, unfortunately, incomplete; but through the courtesy of the Ministry of Munitions it was possible to meet some of the most important men who had had the control of the medical side, and to see the places where the work had been done. It is fortunate that as far as di-nitro-phenol and tri-nitro-toluol are concerned the French consider the problem solved, so that there is a greater degree of completeness than had been hoped for.

The investigation has been particularly interesting on the one hand because di-nitro-phenol is particularly a French explosive, and on the other hand because the troubles which have been recorded in England and in the United States in connection with tri-nitro-toluol have been scarcely seen in France. For this reason the chief discussion in this paper relates to the di-nitro-phenol problems and the methods attempted for their solution, with briefer notes on the French opinions in connection with the toluol derivatives.

Statistics.—While there has been a great variety of explosives manufactured and tried out in France, the main ones have been di-nitro-phenol, tri-nitro-phenol or picric acid, and tri-nitro-toluol. Most of the filling mixtures have been various combinations of these, and the DD or 40–60 mixture of DNP and TNP is the most used. It is not possible at present to get the statistics on the amounts of

the various explosives manufactured or the number of workmen employed except as will be found in the body of the paper, where is given the only accessible information relating to the number of fatal cases in relation to the 10,000-ton production of DNP in 1916–17 and in 1917–18. For the same reasons it is impossible to determine the number of whites, blacks, and yellows, though all were employed, or even to determine the proportions, and in the confusion resulting from the war condition and the changes of groups of men from one place to another, especially true of the Senegalese and the Anamites, it is improbable that such statistics will ever be available for study.

In the same way all the information which has been obtained must be taken with a reservation, as there are various complications which do not appear on the records. It was necessary to move the factory physicians from place to place to care for certain emergencies, so that there is often a lack of continuity in the information, and there was, of course, a great variation in the individual efficiency of the different men.

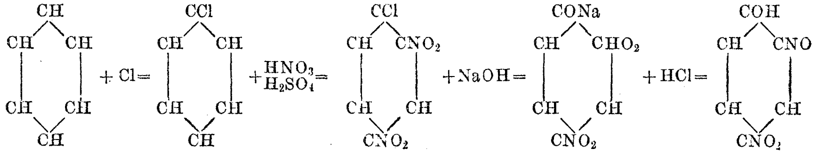
Another point which must be taken into consideration is that there were from time to time, and even from day to day, changes in the demands on the factories, the relative amounts of one or another explosive demanded altering in agreement with the demands from the artillery divisions. In some of the factories these changes necessitated the sudden transfer of men from one melt to another, the change of explosive being often made without change of shop after the cleaning of the vats. Under these conditions the urines of the men who had been on the DNP and were changed to another melt which did not involve DNP were no longer examined, so that the records of examination show apparent wide discrepancies, suggesting incorrectly that the records were improperly kept up. In connection with the Senegalese it must also be remembered that these men were differentiated by numbers and it was found that they had the habit of exchanging numbers or taking the number of a dead man or one who had left, so the records as regards them are practically worthless as *statistics*, though I am inclined to take the personal opinions of the close observers as essentially correct.

With these rather unsatisfactory preliminaries the question of the toxicity of the various explosives can be taken up, and the most important, namely, the di-nitro-phenol, will be first discussed.

I. DI-NITRO-PHENOL INTOXICATION.

While di-nitro-phenol is theoretically a double nitration of phenol, the more usual method of manufacture is from benzene, by the formation of mono-chlor-benzene, which by the treatment with nitric and sulphuric acids is changed to di-nitro-chlor-benzene. Further

treatment by NaOH substitutes NaO for the Cl(NaCl), and the Na is removed by treatment with HCl, leaving the completed di-nitrophenol.



It is obvious that there are six isomeres possible, all of which are known, but the ordinary DNP is the isomere 1–2–4. A further nitration results in the formation of tri-nitro-phenol, which is again possible in six isomeres, of which the most common is the isomere 1–2–4–6 (the ordinary picric acid or melinite).

In the process of the nitration of the chlor-benzene there are formed also certain mono-nitro-chlor-benzenes (notably the para-, with some ortho-) which are not acted on by the NaOH. These must be washed out by a current of steam before the addition of the mineral acids. The finished DNP is a yellow or yellowish-white solid, brownish when improperly made, and with a faint odor of phenol. It can form fine crystals. When pure, the melting point is 114–115 C. It may be sublimed and carried off in aqueous vapor to the amount of about 2–3 grams of DNP to 2 kilograms of steam at 100 C. It is soluble in 21 parts of boiling water, and in about 250 parts of water at 18 C. It is also soluble in alcohol, ether, and chloroform. The reaction is distinctly acid, and crystalline salts are readily obtainable, as for instance, the sodium salt, $C_6H_3(NO_2)_2(ONa)H_2O$.

If there is insufficient treatment with steam there may be a residue of mono-nitro-chlor-benzene, marked by a smell of anise which may be very strong. In the commercial product there may be also traces of chlor-5-nitro-2-phenol. In the nitration of the chlor-benzene there is a small amount of the 3–4 formed, and the NaOH does not attack its atom of Cl, but replaces the NO_2 in the position 3 by a hydroxyl group.

$$C_6H_3\begin{cases}Cl(1)\\ No_2(3)\\ NO_2(4)\end{cases}+2NaOH = C_6H_3\begin{cases}Cl(1)\\ ONa(3)\\ NO_2(4)\end{cases}+NaNO_2\ H_2O$$

It is considered, however, by the French that the various impurities are all less toxic than the DNP itself and can therefore be disregarded as essential factors in the clinical cases. (Appendix 7.)

In the process of manufacture the details are well known, but the essentials, as far as the present investigation is concerned, deal with those parts which admit of the access of the DNP in any form to the various portals of entry of the worker. From the chemical characteristics it may be readily seen that wherever sufficient heat is

used to cause volatilization, or the carrying off of appreciable quantities of the chemicals in water vapor which comes into contact with the workmen, we have one group of possibilities. The other group is in the handling processes, where the solid material comes into contact with the employee in such a way that it may remain on the skin long enough for absorption, or reach more indirectly any of the other portals of entry.

Portals of Entry.

According to the work of Guerbet and others, there are three portals of entry, the skin, the digestive tract, and the respiratory tract. The relative importance of these depends on the character of the work, as in different processes one may be more accessible than another. In general, it is the belief that the skin is the most important, though there are certain series of cases which, if correctly reported, appear to indicate that the respiratory tract is more important. There appears to be no question, however, that all these portals may be used by the intoxicating agent and that through them it may reach the circulation and set up the various specific disorders.

The work of Guerbet and Mayer shows that, in the body, the DNP undergoes certain chemical changes after reaching the blood, or even before, into reduction derivatives, which are of varying complexity. Examination of the blood, the organs, and the urines of fatally intoxicated men shows that while in some the blood and the organs contain unaltered DNP and the urine contains reduction products, in others all contain both the DNP and the reduction products. The main substances found in the urine are as follows:

DNP 1–2–4, eliminated as such;
Amino–2–nitro–4–phenol;
Amino–4–nitro–2–phenol;
Di-amino-phenol.
Nitrogen compounds resulting from the combination of two molecules of amino-nitro-phenol or of di-amino-phenol.

All these except the amino–2–nitro–4–phenol may apparently exist in the urine without any clinical signs of intoxication. This compound, however, while not certainly the proof of intoxication, has always been found in great abundance in the urine of the serious cases. It is accordingly this substance which is used as the basis of the specific test on the urine, known as the Derrien test, or the violet reaction of Derrien, noted elsewhere. (Appendix 1.)

Factors in Susceptibility.

With this diversity of portals of entry, the fact that only a limited number of persons has been affected even under the most unfavorable

working conditions indicates that there must be a very marked variation in susceptibility. Other things being equal, we have the questions of age, sex, and race as the primary possible factors, after which come the more individual characteristics dependent on habits and on physical condition.

Age.—This can practically be neglected, as all the workmen were within the mobilization age and there are no indications that those who were at the later limits of that age were more susceptible than those at the earlier periods, or vice versa. There was no child labor at all. It must be remembered that this refers to the sections of the factory where the actual manufacture and handling of the explosives took place, as there were other sections of the factories where there was no exposure to intoxication.

Sex.—Inasmuch as there was a ruling that no women were to be employed in the dangerous processes, there have been very few employed, and practically all these were in work which was not dangerous. There are no records of any cases of illness among women employed in the jobs exposed to the fumes, vapors, or contact.

Race.—There are certain interesting points in connection with the race factor in susceptibility, as the employees not only came from various parts of France, but also included Annamites and Chinese representing the yellow races, and Senegalese representing the black races. In those factories where the records were carefully kept there was accordingly an opportunity to compare the relative susceptibilities. In general it was found that the Annamites were the least affected, the Senegalese next, and the whites most; but this is to be taken with caution, as other factors of importance may have a very definite bearing. For instance, the Anamites are acknowledged to be the most careful in following the regulations, especially as regards the fumes, and the whites to be the most careless. The question of the relative alcoholism is also very important. It must, however, be noted that among the Senegalese there was frequently a very marked Derrien test of a more or less transitory character, without any serious clinical indications.

At Sorgues, near Avignon, Dr. Senglars states that there were very few cases reported among the Senegalese, although it was not infrequent to find a very marked Derrien test, giving the impression that the blacks are relatively insusceptible. This is, of course, in agreement with the recent experiments in America showing that the colored race has a greater skin resistance to mustard gas than the whites (personal conversation with H. G. Wells), but in the case of the Senegalese the results must be taken with caution. We find that while the whites were under control of the French doctors, the Senegalese were cared for by Colonial doctors, many of whom had comparatively little aptitude for the study of these complex problems,

and cases may easily have been missed. This is the more likely, as the Senegalese were very susceptible to pneumonia and many died of this disease with each change of weather. In the press of work the diagnosis was probably more or less inaccurate, and the general diagnosis of pneumonia was made on inadequate grounds. At least one case was seen on which no diagnosis of DNP intoxication had been made, but which when seen had the characteristic abundant sweats, and when this case was treated by bleeding and other specific methods, it recovered. One of the attendants stated that there had been several similar cases which had been diagnosed and treated as pneumonia and had died under that diagnosis. Other trustworthy observers who have actually made physical examinations of the supposed pneumonia cases report that auscultation was negative and that diagnosis apparently rested entirely on the elevation of temperature and the prostration. *It seems probable that the resistance in the various races was practically identical.*

Alcoholism.—The one point on which there is no disagreement is that the men with an alcoholic history either past or present were by far the most susceptible and had to be weeded out at once. The districts in France which have the reputation of housing the heaviest drinkers also supplied the heaviest toll of DNP intoxications. This statement is not checked by accurate information but it is the opinion of each of the men in charge of the works visited in different parts of the country.

Physical condition.—(*a*) *Lesions of the liver and kidneys.*—This factor is, of course, closely allied to the question of alcoholism, but also includes other cases which have a different etiology. In general, all those persons with the presence of albumin in the urine show a marked susceptibility and are to be included among the serious risks. The actual statistics with regard to the urine are available but it has been the regular practice to remove from the job all men having any urinary troubles apparent in the preliminary urine examinations. There is less evidence in connection with the liver lesions, most of the facts being obtained at post-mortem, and no accurate statistical results can be given.

(*b*) *Respiratory tract lesions.*—There has been no relation of the intoxications traced to these even when the apparent portal of entry has been the lungs, save that tuberculosis is a predisposing factor. This, however, is more probably related to general physical condition than to local lesions.

(*c*) *Digestive tract lesions.*—There is no evidence that preexisting lesions have any bearing on the susceptibility.

(*d*) *Cutaneous tract.*—There is no evidence that lesions of the skin have made the absorption of DNP easier, and, indeed, it appears

probable that such absorption takes place through the normal structures and would be checked rather than aided by lesions.

(*e*) *General physical condition.*—It appears that the resistance in persons with a low grade of physical condition is less than in the healthy, and this is emphasized by the fact that in many cases where the workers have been apparently resistant over long periods of time, if they are sick or overworked they may suddenly develop symptoms. It was partly on this basis that the administration of milk to the workers was started.

Clinical History.

The clinical history has been well worked up by Prof. Etienne Martin, who has had the opportunity to see the cases all over the country, and a summary follows.

1. SUBACUTE INTOXICATION.

This is especially important in calling the attention of the attending physician to the dangers of a more severe attack, enabling prophylactic removal of the worker.

(*a*) *Gastro-intestinal troubles.*—These are the most frequent, and include anorexia, with a white and furred tongue, followed by nausea and vomiting; there may be diarrhea and colics. It is only exceptionally that there is icterus.

(*b*) *General symptoms.*—Workers claim that they have grown thin to a notable extent after several months' work in DNP. Many complain of general weakness with headache and dizziness, with moderate sweats, especially at night. A few days' rest are usually sufficient for a complete cure. The urine shows a positive Derrien, and when this increases day by day or remains at a fairly high point it is an indication that an intoxication of the acute type is about to develop.

2. ACUTE INTOXICATION.

This is generally a sequel to the subacute symptoms, and especially to the gastro-intestinal signs. The onset is sudden, with complaints of having the arms and legs "cut off" (very tired). There is a painful constriction at the base of the chest, and a burning thirst.

The face is pale with slight cyanosis of the lips; there is abundant sweat, and a characteristic agitation and axiety. The respiration is short and dyspnœic, and according to Dr. Senglars at Sorgues, the difficulty is in the *inspiration* in contrast to the *expiratory* difficulty in asthma. There is a moderate elevation of temperature, with a regular pulse. With the occasional exception of a few râles at the bases, the lungs are found to be clear.

There is a marked diminution of the quantity of urine, and a positive Derrien of increasing intensity. Improvement in the case is marked by a marked increase of urine (spoken of by many as a "débacle urinaire").

Removal from work, with a rest cure free from exposure to the intoxicating material is usually followed by a rapid cure. It is to be noted that a single attack of this sort is in no way an immunization, but that these men require careful watching.

3. FULMINATING INTOXICATION.

This is especially noted among alcoholics or persons with renal or hepatic troubles. Death may supervene in a few hours. The usual course of the disease is as follows:

Sudden onset of adynamia, with inability to continue work, or, less frequently, violent colics and abundant diarrhea. After leaving work and going home the condition is aggravated, there is an elevation of temperature up to or even exceeding 40° C., there are abundant sweats, which stain the skin yellow even in the places where there has been no exposure of the skin to the chemicals. There is intense thirst. At times there is an apparent improvement after a bowel or bladder discharge, giving false hope of recovery, while the heart remains regular and auscultation shows nothing except occasional scattered râles. The pupils are contracted, the patient is frightened and excited, and partial or general convulsions follow. This condition of excitement is followed by unconsciousness, coma, and death in a few hours. It is a clinical picture of the end of a fatal uremia case. One of the conspicuous points after death is that the extreme dehydration of the tissues leads to very early rigor mortis, with delay of decomposition of the cadaver.

Some of the cases are even more definite, the workman complaining of the various subacute symptoms, but staying through the work time. He is found somewhere along the road breathing with difficulty, covered with sweat, with a temperature of 41° C. or even 43° C., and dies before anything can be done. In these fatal cases there is a rise of temperature after death, sometimes of several degrees. Urine obtained by catheter shows an intense Derrien.

POST-MORTEM EXAMINATION.

Perhaps the most interesting feature of the post-morten examination is that there are no lesions to be found which are in any way characteristic. The only thing is the acute œdema of the lungs determined by the intoxication of the vasomotor system, obviously the cause of the respiratory difficulty. The microscopic lesions in the liver and kidney cells are inconstant, nor are there anywhere else

any typical changes. It is true that there are readily found in the blood and the organs traces or even more of the DNP and of its derivatives, but this is also true in the nonfatal cases. Moreover, the workmen who die from accidental causes while employed on DNP show the same thing, so no great weight can be placed on it. The most that one can say is that when workers in DNP develop these characteristic symptoms and die after the usual period or are seriously ill and recover under proper treatment the illness is due to the DNP. One may also say that where there are lesions of the renal or hepatic system the resistance is lessened, and this is also true when there is associated tuberculosis, malaria, or chronic rheumatism. The lack of resistance of alcoholics has already been noted and requires only additional emphasis here.

Experimental Work.

Under the Conférence pour l'Etude de la Toxicité des Explosifs (Report in MS.), established in 1915 after the appearance of serious results from the manufacture of DNP, a long and elaborate series of animal experiments were begun by Dr. André Mayer, assistant director of L'Ecole des Hautes Etudes, and completed by him in 1918. The investigation covered experimentation with all sorts of animals, both warm and cold blooded, and also with man, including attempts at therapeusis of various sorts. The author's summary gives an excellent résumé, a translation of which follows:

INTOXICATION IN ANIMALS.

Toxicity of di-nitro-phenol.—The long experience of the Service of Explosives in the manipulation of picric acid, of which hundreds of tons have been made and used without serious cases of intoxication, led to the idea that the nitrated phenols are not violent poisons for the human organism. Accordingly, when the manufacture of di-nitro-phenol was begun and the first cases occurred among the workmen they were put down to impurities in the commercial products. This idea was shown to be incorrect. All the impurities which it was possible to extract and even all the various compounds of benzene formed in the course of the manufacture were found to be less dangerous than the di-nitro-phenol 1–2–4. (Appendices 6 and 7.)

This, then, is a toxic product, no matter how introduced into the animal organization, whether by ingestion, intravenously, subcutaneously, intraperitoneally, or even when rubbed on the skin. This is true for all the animals tested, namely, the horse, dog, rabbit, pigeon, turtle, and frog. In all of these the toxic dose is 0.01 gram per kilo of animal.

Acute experimental intoxication.—Di-nitro-phenol is not only a poison, but a specific poison. The symptoms are characteristic and have a common basis among all the warm-blooded animals. In the first place, there is a considerable exaggeration of the heat-radiation activities as shown by a thermic polypnœa in the dog, vasodilatation

and sweats in the horse. In the second place, in spite of these reactions there is a progressive and considerable elevation of the temperature, which may rise to 45° C. at the time of death. In the third place, there is an immediate rigor mortis.

The fundamental phenomenon is an extensive increase of the combustions, which is neither directly nor indirectly the result of a stimulation of the nervous system. It occurs even in the cold-blooded animals. It bears no relation to an increase of muscular work; it is general and does not appear to result from any indirect action on any special organ, but from a direct action on the general economy. In fatal doses then, the poison appears to be a general stimulant of the cellular oxidations.

The fatal intoxications naturally affect the general nutrition. During the intoxication one notes modifications of the metabolism of sugar (disappearance of the reserves of glycogen, hyperglycemia). One may also suspect variations in the metabolism of the fats (variation of the chemical composition of the various organs), but only to a limited extent. No changes can be seen in the excretion of nitrogenous or saline derivatives.

Furthermore, the fatal intoxications produce functional alterations in certain organs, especially in the liver, whose cytologic structure is transformed (variations of the chondriosome, appearance of abnormal inclusions), together with a change in the chemical composition.

Nonfatal experimental intoxications, if the dose is fairly large, may cause similar symptoms, while with feeble doses these may be entirely absent. But even in these cases the intoxication has an effect on the general nutrition, modifying the nitrogenous and sulphur eliminations. It may also alter the functional value of important organs like the kidney.

Chronic experimental intoxication.—In the same species of animal there is a variable susceptibility to the poison. A few animals succumb to a dose below the normal, and a smaller number resist a dose one and a half times the normal. When a series of nonfatal doses is given, a tolerance to the fatal dose is acquired by the majority of animals. The tolerance is established rapidly and the animals can be daily given a fatal dose for a fresh animal for periods of as long as a month and a half. This indicates that there is no accumulation and that a definite concentration in a single dose is necessary.

There may be no characteristic symptoms in this chronic poisoning, but there are always increases in the exchanges. Sometimes there are polyurias, phosphaturias, and even lesions of the liver and the kidney.

Alteration of the di-nitro-phenol in the body.—In the blood and in the organs are found either the unchanged substance or its derivatives, the amino-nitro-phenols (amino 2 and amino 4) and sometimes the mono-nitro-phenols. *In the case of acute intoxication the amino 2 nitro 4 phenol is always present.*

INTOXICATION IN MAN.

The symptoms of intoxication in man seem closely bound up with those in the animal experiments. In the cases which are to develop fatally there are premonitory malaises, digestive troubles, profuse

sweats, dyspnoea, agitation, elevation of temperature, and after death there is early *rigor mortis*. The intoxication may begin suddenly, and death may occur a few hours later. The symptoms in the severe cases which get well are much the same at first, but the second or third day shows marked improvement with rapid recovery.

At autopsy there are no characteristic lesions. There may be œdema of the lungs; at times a fatty infiltration of the liver. The blood and the organs always contain the DNP or its derivatives and the urine always contains large amounts of amino 2 nitro 4 phenol.

Therapeutics.—All attempts to relieve the conditions by increasing the heat output or by giving antithermics or reducing drugs have no effect. All that can be done is to try to give the body the means of passing the crisis. The best results have been obtained by the use of massive intravenous injections of glucose or inverted sugar.

Pharmacodynamic specificity of DNP 1–2–4.—The administration of ortho or meta mono-nitro-phenol or of picric acid (tri-nitro-phenol) gives none of the above results. The 1–3–4– isomere of the di-nitro-phenol and the para-mono-nitro-phenol do cause them, but only with heavy doses, and even then in a transitory manner. The other isomeres have a very different effect. The 1–2–3– and the 1–3–5 lead to the change of the hemoglobin to methemoglobin. This indicates a very high specificity of the di-nitro-phenol 1–2–4.

As a result of these observations of Mayer, attempts at prevention can be largely removed from an empirical basis.

Mechanical prophylaxis.—Inasmuch as it has been clearly shown that all the usual portals of entry may be available for the entrance of the intoxicant, all possible measures must be taken for preventing the access of the DNP or its derivatives to the workman. In general, the material is in a dangerous condition when in the form of vapor or of dust or when the method of handling brings the solid in contact with the skin. It is also apparent that when the weather is warm the danger is increased. This is probably due to a greater permeability of the skin when there is a tendency to sweat, and to a higher vapor tension.

Whenever possible the processes are to be carried on in a closed apparatus, with the connections closed, so that there will be no release of vapors, and in many cases the improvement of the apparatus has enabled this to be done satisfactorily. On other processes it is still apparently necessary to bring the materials to temperatures where there are vapors and where the workmen must dip out the material or handle it while hot. Even with the use of overhead ventilators, with or without forced draft, there is a good deal of exposure to the vapors, and in such cases there are asbestos curtains around the vats, supposed to be raised only at the time of inspection or handling. In some places, especially where the material is dried in driers or where it is sifted or granulated, there is a good deal of fine dust, which permeates the atmosphere. Here the use of masks is indicated. The personal equation of the workman here, however,

is much as it is in the United States, and the masks are not worn, the curtains are not dropped, and the workman prefers to take his chance. It may be noted in this connection that the Anamites are by far the most careful and the most amenable to the rules, and incidentally it may be recalled that they are the least affected by the poison.

The use of gloves has been suggested, but it has been found that the use of rubber gloves is dangerous, as when the material gets in the glove the skin is macerated and the effect is additionally bad. When gloves are used it is probably better to use washable ones and to see that they are washed at frequent intervals. The use of salves has also been suggested and tried, but none has been found which is sufficiently permanent to be of use.

The *insistence on the cleanliness* of the operative is perhaps the one most effective mechanical means, but offers great difficulty. From the ideal standpoint the following routine should be employed:

Each worker should have two sets of clothes (both outer and under), one of which should be worn in the factory only, should be the property of the factory, and should be cared for and washed by the factory. When the worker enters he is to leave his clothes in one room, pass into another, and put on the working clothes; and whenever he leaves the factory he must leave the working clothes, pass through a bathroom, in which he takes an actual bath, and then put on the clothes which belong to him. In addition, a place other than the workroom must be provided in which he can eat, and the eating of food in any place where the toxic material is handled must be strictly forbidden and the rule enforced. Where possible there should be an enforced rule insisting that the hands be washed and the nails cleaned before eating. The great difficulty is that the workmen object to the use of water either externally or internally, and unless the arrangement is good and a competent man is in charge the baths will be passed by, the hands will not be washed, and food will be eaten on the sly. Another difficulty has been found in France in that the use of printed rules posted in the conspicuous places has immediately resulted in a great amount of neurasthenia, so that after such posting there has been a very large influx of patients to the doctor and a plentiful refusal to work in the explosive as soon as it is known there is danger. When this phase passes the rules are as though they did not exist. In some places it has been found possible to enforce the baths by the arrangement that in order to get from their working clothes to their street clothes it is necessary for the operatives to pass actually through water nearly up to the waist with the shower going above, and by the arrangement, in other places, that when there is no bath there is a reduction of 20 cents in the daily wage and when it is taken there

is a reward of 20 cents, making a prize of 40 cents for the clean and virtuous.

Broadly speaking, the efforts at cleanliness are at best only partial and act as adjuvants to the mechanical devices for the prevention of contact. The best means of prevention are probably those under the following heading:

Medical prophylaxis.—As noted earlier in this paper, it has been found that the reaction of Derrien is a fair indicator of the susceptibility of the worker, and in France it has been especially on this basis that the medical work has been done. For the proper performance of the test and for the carrying out of the subsequent treatment it is necessary to have a man skilled in urine examinations and with the proper laboratory equipment, one who is to work in association with a factory physician, to whom all the urinary records go for the determination of the further activities in each case. The factory physician should have facilities for complete physical examination and should, of course, be competent in diagnosis to differentiate from other ailments and to classify the symptoms noted above as suggestive of DNP poisoning. There should also be readily accessible a hospital or infirmary, where any serious cases could be treated at once. If these matters are cared for, the system is as follows:

At entrance there is a general medical examination as far as possible, with information as to history of alcoholism and of syphilis or kidney troubles, and a complete urine examination to determine the presence of any weakness of the kidneys. As far as possible, all men having any of the earlier noted predispositions should be refused admission. This is often impracticable, but, even so, the history will indicate which men need watching. Men with a history of malaria and with enlarged spleens and livers are also bad subjects, especially so if alcoholic. After the preliminary selection of the men there should be a weekly round by the doctor, during which he can note the conditions and see if any of the men are suffering from ailments which they are not reporting. This will also afford an opportunity to educate the men in the essentials and to show the reasons for the necessary care. At these visits he will also examine the urinary records for the positive Derriens. It is the opinion of Martin that *where the dusts and the vapors are removed, where the workers are properly selected, and where cleanliness is enforced, there should be no positive Derriens.* This, in other words, says that the presence of a Derrien in men working in a theoretically correctly run shop means that there is a fault in technic, either in the mechan-

ical devices or the hygiene of the workman, or that there has been a change in the personal equation of the individual. If a positive test is found and persists for several days, or increases in intensity, the workman must be examined at once, kept under surveillance, and removed from the shop as soon as there are any of the early symptoms, especially if there is any elevation of the temperature. "The progressive daily increase in the intensity of a Derrien is to be considered as a sign of intolerance." Inasmuch as there is no rule as to the exact relation between the intensity of the test and the danger to the individual, the intensity should not be allowed to pass the fourth or fifth degree (Appendix 1). The main value is the information to the attending doctor.

Inasmuch as for the establishment of a disintoxication there is a minimum of eight days, it has been suggested that there should be, as far as possible, a rotation of service so that the men will not work in the dangerous divisions for more than two weeks at a time, with a subsequent change for two weeks to a shop free from danger. This will also prevent the development of the cases in which after a period of freedom there is a reaction following overwork of an intensive character. There have been technical difficulties in this connection, and, as a matter of fact, it has been left largely to the individual factories to settle.

It should also be the duty of the visiting physician to see that the various rules are enforced, that ventilation and the withdrawal of the vapors and dusts are being efficiently carried on, that the clothing which is supplied to the workmen is of a suitable character, as, for instance, in the wooden sabots, which are the habitual footgear in France, there must be ankle pieces preventing the dust from falling in and being macerated into the skin of the feet. This, of course, has been noted in connection with the TNT workers in England. Against the powders and dusts of the DNP the Tissot mask of the special make for the munitions has been recommended.

Treatment.—In all simple cases the withdrawal of the workman from the danger area is sufficient. He should be kept out at least until the test in the urine becomes negative. In the more serious cases the treatment is still of the symptomatic character, as there is as yet no special antidote available. The most successful treatment consists in the attempt to get rid of the poison as fast as possible by the use of purgative, and by abundant bleeding followed by injections of glucose solutions. Martin believes that the bleeding is of value not only as a diluent of the poison, but also from its action as a vaso-constrictant, in neutralizing the vaso dilatation effect of the DNP. In connection with this treatment the administration by the

mouth of alkaline drinks and milk is indicated. The use of the latter is, apparently, mainly because of its value as a rapid nutritional factor, as I have found no one who offered any reason why it might be of value otherwise. The use of morphine as a check on the excitement and dyspnœa is also indicated. This treatment should be given in the hospital and the patient should be watched carefully till safe.

Martin considers the milk treatment as of no value, except as a food, and classes the demand for it and the violent objections to its disuse in the same class with the corresponding use and disuse of coffee in the works where there was nitroglycerine, and the coffee was used empirically and then abandoned. The protests were profuse, but the withdrawal had no ill effects; in fact the contrary, as the habit which had developed of taking so much coffee had produced bad physiological effects, and had actually reduced the efficiency.

Systematic Activities of the French Government.

The question of munitions intoxications was taken up very seriously by the Ministry of Munitions, and it is owing to their appreciation of the efforts of their experts appointed in 1915 that much of the improvement in the manufacturing conditions and the resultant improvement in the health of the employees has been possible. In all my inquiries they have shown the greatest courtesy and consideration, and I desire particularly to express my appreciation of the help of the following:

Inspector General of Munitions Vieilles.
Dr. Etienne Martin, Professor of Legal Medicine at Lyon.
Dr. André Mayer, Assistant Director in l'Ecole des Hautes Etudes.
Dr. Guerbet, Secretary to the Munitions Intoxications Commission.
Mr. Lheure, Director of the Manufacture of Explosives.
Dr. Senglars, Physician in charge of factory at Sorgues.

A brief account of the history and development of the commission follows, the original report of which is in MS.

Soon after the appearance of the cases of intoxication in 1915, there was formed, under the auspices of the Ministry of Munitions, a Commission for the Study of the Toxicity of Explosives. There was a large personnel established with very competent specialists and investigators, and a report was presented in June, 1918, covering the work of the commission. The following is a brief account of the plans and accomplishments:

As soon as a substance is noted as dangerous or likely to be dangerous, a systematic study is made and distributed to the members. At the same time investigations are carried on in the factories as a routine measure. Abstracts are made of the foreign work

which are studied by the conference. (Then follows a brief statement of the results obtained by Guerbet and Mayer and Martin, noted elsewhere in this paper.) Instructions were given in a special course at the Collège de France to the men who were appointed as specialists, and these men were then distributed to the various factories. The visiting physicians were ordered to make clinical examinations of the workmen, with regular routine visits, and specially trained pharmacists were appointed for the urine examinations. It was made their duty to examine frequently the urines of the workmen, every two days in hot weather, less frequently in cold weather, and to report the results to the physician in charge.

In addition, measures for the general hygiene of the workers were established, including the rotation of service and obligatory shower baths. The desiccators were given up and the product was manipulated in a moist condition to avoid dust, the fusion vats were covered with an asbestos curtain and ventilators were established above them, and the granulation which followed the fusion process and which was formerly a hand process, was made a mechanical one. There are in process of substitution for the granulation, which is dusty at the best, other procedures such as "drageification," resulting in somewhat larger masses and performed by the "tonnes Landrin," or poured in slabs, by the "cylindres Tesmart." Similar regulations and changes have been arranged for the loading factories.

Modifications of the law of 1898 on industrial accidents were made, which have the effect of adding the munitions intoxications to the other formerly listed accidents. Other studies were undertaken on the intoxications by nitrous gases and vapors, and the use of the army gas masks, with modifications in the metal parts, was recommended. A number of these were accordingly made, and the workmen are provided with them.

The results of these activities have been satisfactory, and while the records are not of a sort which gives accurate statistics of the morbidity and mortality in comparison with the numbers employed, by means of comparing the number of deaths per 10,000 manufactured tons in the year prior to the establishment of these improvements with the number in the year following, some idea can be obtained.

Period.	Deaths.	Tons of DNP and mixture DD manufactured.	Deaths per 10,000 tons.
May, 1916, to May, 1917	31	19,100	16.3
May, 1917, to May, 1918	5	40,700	1.2

Through the courtesy of Dr. Guerbet, the actual records of the various factories in connection with the use and results of the Derrien tests were placed at my disposal and served to confirm the statements of the various men to whom I am indebted for my information. This is the more valuable, as the records had not yet been analyzed in any detail and no graphs had been made.

The material available included the semimonthly records of the Derrien tests on sheets showing the actual number made during these periods, covering about 15 months, with two summers and one winter, and showing also the number of tests for each type of

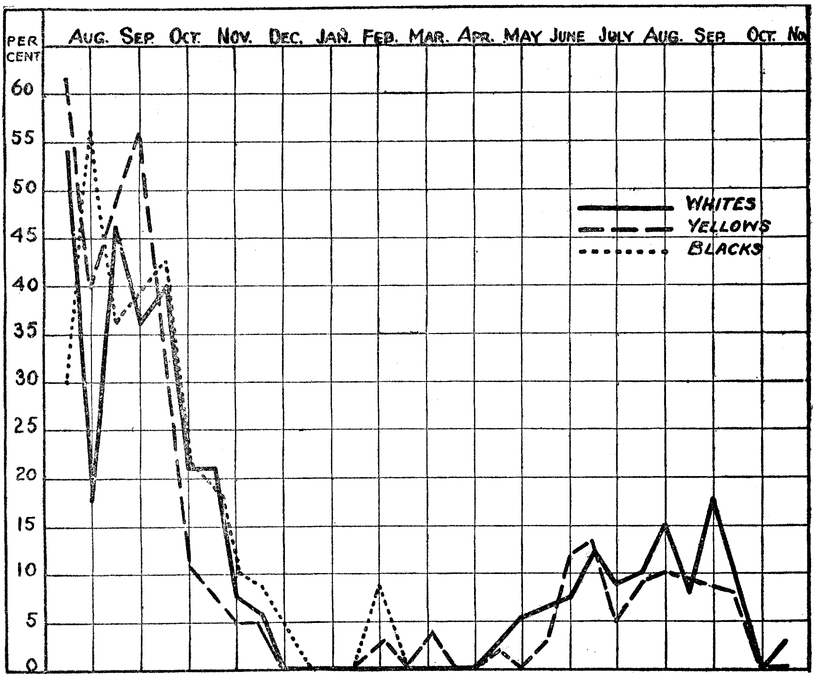


CHART 1.—(Sorgues Works) Percentage of positive tests in the Derrien examinations of urines, corrected in proportion to the numbers in each color actually tested at the time. August, 1917, to November, 1918.

employee by race and the number of clinical cases in each period which bore relation to the positive Derrien tests. It is, of course, unfortunate that in the earlier periods, in which the highest number of cases of illness occurred, the system had not been as yet evolved, so that there are no accurate records of these at present available.

As noted earlier, it is not possible to ascertain the number of employees who were actually employed at the different periods, and the best that could be done was to correct the positive tests in connection with the number of whites, yellows, and blacks whose urines were examined in the given periods. After this correction it will be seen that in general the curves for the colors approximate closely,

justifying the general impression that there is no essential difference in racial susceptibility. It will also be noted that the percentage of positive tests increases in summer and falls in winter, forming a very characteristic curve. For a variety of reasons there were rather fewer tests actually made in the winter than in the summer months, but there were enough to carry out the percentage

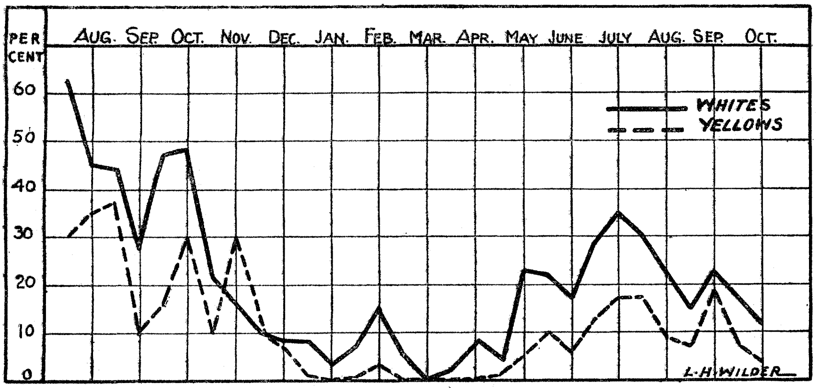


CHART 2.—(Bassen's Works) Percentage of positive tests in the Derrien examinations of urines in relation to the total number of actual chemical tests in the same period. This diagram gives the actual totals corrected to correspond with the relative number of whites and yellows actually tested at the corresponding periods.

scheme with a fair degree of accuracy. Chart I deals with the works at Sorgues, near Avignon, which were in charge of Dr. Senglars, and in which a large amount of DNP and TNP was constantly being manufactured. The two most conspicuous features are the notable difference in the numbers of positive Derriens in the two summer periods, thought to be due to the greater care in the selection of the employees and the other factors spoken of earlier in

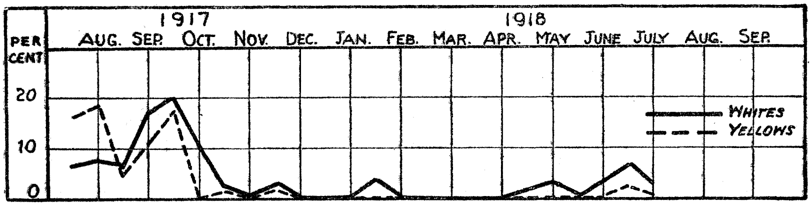


CHART 3.—(Bassen's Works) Actual number of clinical cases noted in the workers tested in 1917 and 1918. This diagram is based on actual figures for whites and yellows without regard to the relative number of each color actually employed at a given period.

this paper, and the close approximation of the curves for the three races.

Chart II is a similar series for the Bassens works, near Marseille, where the conditions were less good, and shows essentially the same points. In Chart III, also dealing with Bassens, where there were a good many clinical cases, the relative number of actual clinical

cases analyzed according to color show a marked reduction in the second year, due again to the improvement in care and in conditions of work. At these works there were practically no blacks employed, so there has been no notation of records.

II. INTOXICATION BY OTHER EXPLOSIVES IN ADDITION TO DI-NITRO-PHENOL.

The main explosives which the French have used in the course of the war have been tri-nitro-phenol and tri-nitro-toluene and combinations of these with each other and with di-nitro-phenol.

Picric acid or tri-nitro-phenol or melinite.—This was the favorite in prewar times and the main supply was obtained from Germany, so a new phenol industry had to be set up. It was therefore possible to get an idea as to the toxicity of this chemical through all the procedures of manufacturing and handling. The result may be briefly summarized as follows: With the exception of the staining of the skin of the operatives, there have been no serious results or even serious cases of sickness. In the experimental work done at Lumières in September, 1916, the dose by mouth of melinite necessary for the death of a guinea pig was taken as unity, and it was found that one-fifth or less of DNP had the same effect, while the various toluenes required two or four times the dose. Through all the experiences it has not only been considered that there is no danger, but the TNP melts have been used as resting places for the workers who have the early intoxications with DNP. The intoxications from this may therefore be dismissed as certainly of little importance.

Many of the explosives used in quantities changing according to the requests of the department of munitions have been varying mixtures of DNP, TNT, and TNP; it has been found that the toxicity had been more marked in all cases where there was most DNP, though there could be no scale established. In general, in fact, the presence of DNP in any notable amount in a mixture was about as dangerous as where it was handled alone. The degree of the danger, of course, was in direct relation to the amount accessible to absorption.

Di-nitro-toluene.—The process of manufacture results in the formation of several isomeres, which the French consider as the toxic part. These are rather oily in character and by suitable processes can be taken out, leaving a purified substance which is practically nontoxic. Perhaps the chief complication of the purification process is that the removal of the oily parts makes the material much dustier, so there is some irritation to the mucous membranes and a possibility of absorption. It is clear, however, that if the toxicity is removed by the process the dust is a nuisance rather than a danger.

During the process of removal of the oily products, the workers handling the blocks were often made ill, as were also those exposed to the vapors from the washing process. In one shop there were 25 workmen and at times half of these were incapacitated. This led to a study of the oils isomeric to the DNT and the following information was obtained:

There are four isomeres, all of which are represented in the oily substances which must be removed for the purification. Of these the 2–6, 2–5, 3–4 are the most frequent. Moreover, if the nitration has been incomplete, there is also some metal MNT found in the oil. This is the most difficult of the MNT isomeres to nitrify, so it is clear why it appears in the oil. In the work at St. Fons it was found that there was about 25 per cent of undesirable oil in the DNT, which was thrown out into the sewers without attempt at salvage, and was in fact called "Huile d'égout."

The French thus believe that it is practicable to obtain a pure DNT, with low toxicity, as a base for the final nitration.

Tri-nitro-toluene.—While this was less used among the French than among the English and Americans, there was a great deal made, at least in sufficient amount to expose many workers to its effects. The operatives were no more cleanly than the English and Americans, yet in France the experience has differed from that of the other countries. Contrary to the English idea, the French consider the manufacture of TNT to be essentially safe and have had few disabilities. There have not been recorded more than two cases of jaundice with fatal outcome, and while it is of course possible that in the hurry of war conditions there may have been some cases missed, the general statement is that in the case of deaths of the operatives, the inquiries set up by the authorities were very rigid. What is perhaps more important is that the French claim that there has been very little disability involving *loss of time* among the workers so that it has not been considered necessary to have change of occupation or any special medical investigations.

They consider that the purification by "sulphitization" is essential for the removal of the asymmetric isomeres, and for the removal of the tetra-nitro-methane, now known to be poisonous.

Where the purification has been properly carried out, the French consider that the toxicity is small, as was formerly considered to be the case, and are of the opinion that the troubles which have been experienced in England, and to a somewhat less extent in the United States, are due to the fact that the toxic isomeres have been left in to a greater or less extent. In this connection it may be noted that in the present process in England the sulphitization is used with some care, and that there are many fewer cases of intoxication. Moreover, where these do occur, they are less in degree than in the earlier

days. Like all statistics where there are several features to be considered, one must be cautious, but it certainly appears to be *post hoc*, whether *propter hoc* or not, as the various other methods of control have been introduced at about the same time.

In view of their disagreement, it is not out of place to bring in at this point a translation of the French process of the manufacture of tri-nitro-toluene.

Manufacture of Trinitrotoluene.

The manufacture of trinitrotoluene involves three processes of nitrification and one of purification, and the finished product should be 99 per cent symmetrical TNT of the 2–4–6 variety.

Mono-nitration.—It is necessary to use 2 to 5 per cent more HNO_3 than is required by the equation, which is as follows:

$$C_6H_5CH_3 + HNO_3 = C_6H_4 \begin{matrix} CH_3 \\ NO_2 \end{matrix} H_2O$$

and in the process enough H_2SO_4 must be used so that the residual acid after the nitration will contain a maximum of 30 per cent water. The temperature adopted is 35° to 40° C.

The result contains a mixture of the three isomeres—ortho, meta, and para—in about the proportions of 60, 5, 35 per cent. It solidifies at +3° C. by the crystallization of para-nitro-toluene.

Di-nitration.—The nitration of this crude mono-nitro-toluene gives a mixture of isomeric di-nitro-toluene, melting at 56°, if free from mono- and tri-nitro-toluene. It contains 2–4, with a melting point of 70.5° derived from the nitration of the ortho and para mono-nitro-toluenes, and forming the greater part of the mixture. It contains also 2–6, melting at 61°, formed at the same time as the 2–4 at the expense of the ortho-mono-nitro-toluene. In addition there is 2–5, melting at 52.5°, and 3–4, melting at 60°, both of which are formed from the meta-mono-nitro-toluol, and it is these that cause the oily character of the crude stuff.

The oxidation is more intense than in the mono-nitration, with the destruction of some organic matter and with the change of some of the nitric acid into the nitrous products. It is therefore necessary to use about 10 per cent more HNO_3 than is called for in the formula:

$$C_6H_4 \begin{matrix} CH_3 \\ NO_3 \end{matrix} + H\ O_3 = C_6H^3 \begin{matrix} CH_3 \\ NO_2 \\ NO_2 \end{matrix} + H_2O$$

The H_2SO_4 must be in sufficient excess to have at least 74 per cent of it left in the residuary acid.

For this di-nitration the residuary acids left after the tri-nitration are strong enough in H_2SO_4 but require the addition of HNO_3

and are employed for di-nitration of the mono-nitrate in quantities equal to those left from the tri-nitration of the amount of di-nitro-toluol *desired.* The temperature of the process is 50°–55°, and the ultimate heating is 90° C.

Tri-nitration.—Inasmuch as the product comes from the nitration of a mixture of isomeres, it also is a mixture as follows:

MONO-NITROS	DI-NITROS	TRI-NITROS	MELTS AT
Para	2–4	2–4–6 alpha	80.8° C
Ortho	2–6		
	3–4	2–3–4 beta	112.0° C
Meta	2–5	2–4–5 gamma	104.0° C

These are found in the proportion of about 95 per cent of the 2–4–6 and 4 to 5 per cent of the others, among which the 2–4–5 is in the largest amount. There are also small amounts of oxidation products of an acid type, and traces of tetra-nitro-methane, of which these mixtures possess the characteristic smell.

The process is accompanied by an oxidation which will destroy about 5 per cent of the product and change a notable part of the nitric acid into nitrous products. The transformation needs about 120 per cent more nitric acid than is called for in the formula, to compensate for the loss of nitric acid due to oxidation, and for the additional loss of acid due to its distillation in the course of the process.

$$C_6H_3\begin{cases}CH_3\\NO_2\\NO_2\end{cases} + HNO_3 = C_6H_2\begin{cases}CH_3\\NO_2\\NO_2\\NO_2\end{cases} + H_2O$$

The sulpho-nitric acid used in this stage of the process must be *absolutely anhydric.* The amount of H_2SO_4 must be sufficient to leave 88 per cent in the residuary acid, which, as noted earlier, can then be used for the di-nitration with the addition of adequate HNO_3. The figure is not absolutely accurate on account of the abundant nitrous products whose activity is not clear. They appear, however, to reduce the activity of the bath in a manner analogous to that of water. In the process the temperature is 80° to 105° C, and the ultimate heat 120° C.

Purification.—The *asymmetric* isomeres must be removed, as they are oily and prevent perfect transmission of the explosion. The process is known as *sulphitization.*

Sodium sulphite in aqueous solution acts readily on these isomeres when diluted in a large amount of the *symmetric* forms, and changes them into di-nitro-sulphonic derivatives. The detail of the process is shown in the formula:

$$CH_3\,C_6H_2 \begin{cases} NO_2 \\ NO_2 \\ NO_2 \end{cases} + Na_2SO_3 = CH_3C_6H_2 \begin{cases} NO_2 \\ NO_2 \\ NaSO_3 \end{cases} + NaNO_2$$

The acid oxidation products which exist in traces are also eliminated by this treatment, and the tetra-nitro-methane is also broken up, as noted elsewhere. (Appendix 4.)

To prevent attack on the *symmetric* tri-nitro-toluene the reaction must take place at a temperature low enough for this to be in the solid form. Moreover, to get a good result the sulphite must work on the crude tri-nitro-toluene when this is in a finely divided condition and preferably crystalline. By cooling the crude material while it is in active agitation in its own weight of water, it crystallizes in fine needles and is in suitable form for the reaction. This takes place best at about 25° or a little higher.

It is essential to have a crude tri-nitro-toluene free from di-nitro-toluene and from xylite in order to obtain a purified tri-nitro-toluene with a melting point above 80° C.

Thus according to the French ideas the chief stages of danger in the manufacture of the tri-nitro-toluene are in the intermediate stages when the nitration is not completed, the di-nitro-stage, on account of the oily isomeres, and in the final stages of the finished product, when the last traces of the impurities are being carried off. After this, the toxicity of the material is, in their opinion, minimal. The danger from tetra-nitro-methane is taken up in detail, and while they now acknowledge the toxicity, they claim that the sulphitization removes all this substance and that there should be no trouble from it in the finished product. (Appendix 4.)

Other nitrated bodies.—The results obtained in these various investigations led to a further series of studies of the various bodies used in the manufacture of the explosives and of the by-products resulting from the processes. In general, the two points studied were the minimum fatal doses and the relation of intoxication to the vasomotor phenomena.

Samples of a variety of materials were obtained, including—

di-nitro-anisol,
tri-nitro-anisol,
chloro-benzene,
di-nitro-chlor-benzene,
para-nitro-chlor-benzene,

which were compared in the same series of experiments to—

di-nitro-phenol 2–4,
tri-nitro-phenol,
di-nitro-toluene 2–4,
di-nitro-toluene 2–6,

as shown in the following chart taken from the article by Mayer, on the toxicity of nitrated compounds, found as Appendix 7.

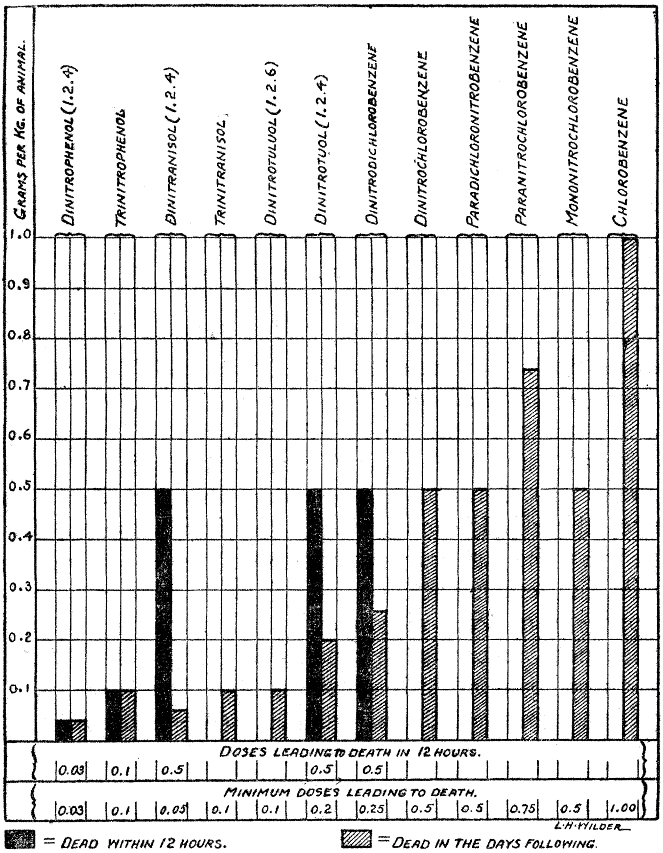


CHART 4.—Minimum fatal dose (for the dog) of different derivatives of benzene in subcutaneous injections in oil.

References.

Inasmuch as practically all of the material used in the preparation of this paper is either still in MS or is printed in a form which is not available for general distribution, and will not be accessible to the ordinary student for an indefinite time, the essentials have been translated and added to the article as appendices and references have been made to them in the text. For convenience, however, a list is appended, with the titles and the position in the appendix.

1. L'expertise chimique dans les cas d'intoxication par le di-nitro-phénol. Recherche Toxicologique du Di-nitro-phenol et de l'Acide Picrique par M. le Dr. Guerbet. Paris, 1918. Ministère de l'armement et des fabrications de guerre.
2. Conférence pour l'étude de la Toxicité des Explosifs. Paris, 1917. Ministère de l'armement et des fabrications de guerre.
   Properties of di-nitro-phénol. M. Blaise.
   Toxicity of di-nitro-phenol. Dr. André Mayer.
   Portals of entry. Transformation and elimination of the poison. Investigations of the derivatives in the urine. Dr. Guerbet.
   Symptomatology, diagnosis, prophylaxis, treatment. Dr. Martin.
3. Experimental studies on the toxic properties of di-nitro-phenol and other nitrated benzene derivatives.
   Manuscript. Animal Experimentation. Dr. Mayer. An extensive and important work. Summary given in body of article.
4. Intoxication par le Di-nitro-toluene. Kovache. Appendix 2. MS.
5. Intoxication par le Tolite. Kovache. Appendix 3. MS.
6. Note sur l'elimination des Tolites Brutes d'un produit toxique. Le Tetranitro-methane. Muraow. MS. Appendix 4.
7. Sur les effets vasculaires de l'inhalation des Vapeurs Nitrés. André Mayer. MS. Appendix 5.
8. Sur les effets toxiques des Huiles de Xylene et des Toluenes Nitrés. André Mayer. MS. Appendix 6.
9. Sur la toxicité de quelques dérivés du Benzene. Phenol et Toluols Nitrés Industriels. André Mayer. MS. Appendix 7.
10. Rapport sur la Création, le Fonctionnement et les travaux de la Conférence pour l'étude de la Toxicité des Explosifs. MS. Appendix 8.

APPENDIX 1.

Reaction of Derrien.

This is the reaction used by the French in the study of the urines in di-nitro-phenol intoxications. The formation of an "azoic" by diazotation of the amino-nitro-phenols and copulation with the beta naphthol in ammoniacal solution has been used by Prof. Derrien to identify picramic acid in the urine. The "reaction of Derrien" implies the finding of an "azoic" soluble in ordinary ether and giving a violet purple color to the solution. This reaction was later extended to the investigation of other amin derivatives of the nitrophenols such as amino 2 nitro 4 phenol, and amino 4 nitro 2 phenol, which give "azoics" of various tints. The expression "Derrien's reaction" must, therefore, in this connection, be understood to refer only to the original reaction, or the general term "azoreaction" must be substituted. For the benefit of those who desire to follow the essential chemistry of the process more carefully, a translation of the explanations of Guerbet will be found in the appendix. In the application of the test the "azoreaction" is obtained by "diazoting" an amino-nitro-phenol, by "copulating" the diazoic thus obtained with an ammoniacal solution of beta naphthol, and finally by recovering in an ethereal solution the azotic coloring matter which has been formed.

DERRIEN REACTION: TECHNIQUE.

To urine recently passed	10 cc.
Add 10 per cent H_2SO_4	1 cc.
Then 0.50 per cent $NaNO_2$	1 cc.

shake and leave in the dark for five minutes. In another tube with a capacity of at least 25 cc. place—

Freshly made beta naphthol, 0.5 per cent solution in (22 B) ammonia	2 cc.

Pour the treated urine into the beta naphthol, shake, allow to stand a minute or so and add—

Ordinary ether	10 cc.

Close the mouth of the tube with the finger, shake well, then cork with cork and allow the separation of the ethereal solution to take place. The color of this portion is the only one to be considered, the color of the aqueous portion having no importance.

INTERPRETATION.

If the color of the ether is violet, or wine color, or orange red, the reaction is said to be positive.

If it is colorless or yellow the reaction is said to be negative.

In an arbitrary way the degree of the reaction can be estimated in the following manner:

Make up a stock solution of—

Potassium permanganate	0.20 gms.
Potassium bichromate	.75 gms.
Distilled water	1,000.00 gms.

In 12 tubes of the same type as those used for the Derrien test, make dilutions as follows:

Stock.	Water.	Corresponds to Type—
0.5	20	I.
.5	15	II.
.5	12	III.
1.0	17	IV.
1.0	13	V.
2.0	18	VI.
3.0	18	VII.
3.0	12	VIII.
5.0	15	IX.
7.0	14	X.
8.0	8	XI.
15.0	0	XII.

It is, of course, to be understood that this is not exact, but it is accurate enough to be convenient and usable.

The stock solution is very stable under ordinary precautions but the dilutions must be made up fresh for each series, as they are good only for four or five hours. The tubes for the dilutions should be washed with sulphuric acid and permanganate of potash and rinsed in distilled water.

CHEMISTRY OF AZOREACTION.

When the salt of a primary aromatic amine is treated by nitric acid (acide azoteux), a " diazoic " or " salt of diazonium " is formed. This is called " diazotation." If this salt is combined with a phenol, an " azoic " (oxyazoic) coloring matter is obtained. This reaction is a copulation, and is obtained by the use of the phenol in alkaline solution. The azoics whose formation allows the identification of the amino-nitro-phenols under discussion are obtained by copulation with beta naphthol, and are known as " azonaphtols." In reactions they act as acids with a strength depending on the number of NO_2 groups in the particular amino-nitro-phenol from which they started. It is the hydroxyl atom of the amino-nitro-phenol which plays the rôle of acid, and when this hydroxyl group is combined with a base—ammonia in the Derrien test—the azoic is in general very highly colored. This is notably the case in the azo-beta-naphthols corresponding to the amino 2 nitro 4 phenol and to picramic acid. When, however, the hydroxyl is set free by the action of an acid it is colorless or yellowish.

The freeing of the hydroxyl group combined with a base is the easier to obtain in direct proportion to the diminution of the NO_2 groups and the increase of the strength of the acid. Thus the azo-beta naphthol which corresponds to the amino 2 nitro 4 phenol is easily liberated from its base by dilute acetic acid, while that which corresponds to picramic acid requires dilute sulphuric, acetic acid having no effect.

The azo-beta-naphthols obtained from picramic acid, from amino 2 nitro 4 phenol, and from amino 4 nitro 2 phenol, are soluble in water in the absence of ammoniacal salts, and under these conditions do not give up their coloring matter to ether. But in the presence of ammoniacal salts the azoics are precipitated in the aqueous solution and readily taken up by the ether. This is the condition which obtains in the azo reaction, and there is a tendency to have the color enhanced by the increase of the ammoniacal salts.

NOTES ON THE REACTION.

The salt of diazonium is affected by light and must be protected till ready for the second part of the reaction, and must not be heated, as it is altered by heat. The naphthol solution must be freshly made and filtered, and must be colorless. On standing there is a yellow color formed which is soluble in the ether and interferes with the accuracy of the reaction. It is important to pour the diazo solution into the naphthol solution, as if this process is reversed there may occur the formation of nitroso-beta-naphthol, which interferes with the reaction.

The delicacy of the reaction as applied to the amino-nitro-phenols is very great, mounting to one in one million, and is far more delicate than any other test which has been brought forward.

The amino 2 nitro 4 phenol and picramic acid gives azoics whose colors in ethereal solutions are very difficult to distinguish, varying in color from wine red to permanganate violet.

The amino 4 nitro 2 phenol gives an azoic whose color in the ethereal solution is a more or less orange yellow.

The authors have carried out in some detail the tests necessary for the further determination of the various compounds in the blood and organs and the differentiation in detail in the urines, but for the purposes of this paper this detail is unnecessary. It is to be hoped that the original work of Guerbet and of Mayer, now in MSS., will soon be published, as there is much detail of interest which can not be brought forward without a practically complete translation.

APPENDIX 2.

Intoxication by Di-Nitro-Toluene.

During the period of March to October, 1915, the factory of the Society for Chemical Industry at Bale, branch of Saint Fons, produced about 100 tons of drained di-nitro-toluene.

The drainage consists in enriching the di-nitro-toluene 2–4, by draining off the greater part of the oily products which accompany this isomere in the crude di-nitro-toluene.

To effect this operation the crude, washed di-nitro-toluene was poured into buckets of iron and left to solidify slowly. After which the cakes of di-nitro were broken up and left for 24 hours on a perforated stage in a room at a temperature of 25°.

We have seen several cases of intoxication caused by the washing and the draining of the di-nitro-toluene. This last operation was particularly dangerous, inasmuch as it necessitated the handling of the cakes of di-nitro-toluene. On several occasions we have had 50 per cent of our personnel (25 workmen) incapacitated.

COMPOSITION OF THE DRAINED OIL.

The oil produced by the draining of the di-nitro-toluene is a mixture of the 4 di-nitro-toluenes 2–4, 2–6, 2–5, 3–4, but much richer in the isomeres 2–6, 2–5, and 3–4 than the crude di-nitro-toluene.

If the dinitration has been imperfect and the di-nitro contains mono-nitro-toluene, the latter accumulates in the drained oil. As the meta-nitro-toluene is the most difficult isomere to nitrate of the three mono-nitro-toluenes (ortho, meta, and para), it is admitted that it predominates in the mono-nitro-toluene, is likely to exist in the imperfectly nitrated di-nitro, and therefore it passes into the waste oil supplied by this same di-nitro-toluene.

Under the conditions in which the drainage of di-nitro was practiced at the factory at Bale at St. Fons, 100 parts of crude di-nitro-toluene (M. P. 55°, 56°) gave about 25 parts of oil and 75 parts of drained di-nitro (M. P. 62°, 63°).

ABSORPTION OF THE DI-NITRO-TOLUENE BY THE ORGANS.

It may, in our opinion, be effected in three different ways:

1. Through the respiratory tracts, caused by remaining in the workshops where vapors of the products exist, such as the—

(*a*) Draining room—the di-nitro-toluene and its oils have a vapor tension appreciable at ordinary temperature;

(*b*) Washing room—the watery vapor which escapes from the vats carries small quantities of the product.

2. Through the digestive tracts, caused by eating without having carefully washed the hands and nails.

3. Through the skin, caused by handling the product, impregnating the clothing with di-nitro, and especially the socks, which are in direct contact with the skin; and by handling tools impregnated with di-nitro-toluene (handles of shovels, etc.).

SYMPTOMS OF THE INTOXICATION.

Cyanosis: Violet blue coloration of the lips and lobes of the ears, face livid (as though seen by the light of a mercury lamp or sodium light).

Dizziness (the patient appears drunk).

Tendency to sleep, headache, dyspnœa, brown urines.

We have always seen cyanosis even before the patient felt indisposed.

Several workmen employed in the drainage of di-nitro have suffered pains in the joints, especially in the knees; these pains continued for several months after the men had left the factory at Bale and had given up the manufacture of di-nitro-toluene.

One of our workmen (E. D.) suffered eye trouble (weakening of the sight), but it is possible that this man suffered from some other disease having no connection with the intoxication.

It has been noticed that some people offer more resistance than others to the action of the product. Alcoholic subjects have very little resistance.

The accidents caused by the raw di-nitro-toluene are much more frequent in summer than in winter. We have never had any fatal accidents; the greater number of patients recovered after two or three days, and much more rapidly if they left work as soon as the first symptoms appeared.

MEASURES TAKEN TO COMBAT THE INTOXICATION.

General measures: As soon as cyanosis appears have the workman leave the workroom and walk in the open air.

Fight the tendency to sleep by having workman drink coffee.

Ventilate the workroom.

Give no alcohol—no wine—give milk.

Avoid touching the product with the hands. Our workmen have always worn rubber gloves, but these become dangerous if the product penetrates to the inside. This often happens, in which case the skin of the hands fairly macerates with the noxious substance.

Attention to the personal cleanliness of the workmen: Washing the hands with carbonate of soda before leaving the workroom at meal times.

No eating in workroom.

Special clothes for working.

Outdoor clothes and knapsacks containing food should be hung in the cloakroom and not in a corner of the workroom.

St. Chamas, May 27, 1918.
Military Technical Agent.
Signed: KOVACHE.

APPENDIX 3.

Intoxication by TNT.

During the stay of a year at the factory of Neuville (1916) we have to report the death of only one workman affected by the grinding of the product; but the autopsy proved that this man had been alcoholic (cirrhosis of the liver).

The male and the female workers affected by the grinding of crude TNT show a livid tint of the face, but never complain of pains.

The grinding of TNT makes no perceptible dust, the product having a greasy consistency, but, on the other hand, it is made unpleasant by the presence of tetra-nitro-methane, which irritates the eyes. This substance is given off by the crude TNT during grinding, which increases the surface of the product exposed to the air. It has an appreciable vapor tension, for TNT, ground a certain time and exposed to the air, no longer smells, or irritates the eyes.

It seems that in the American factories the odor of crude TNT and its tear-producing properties have seriously discommoded the workers, because, ever since November, 1915, it is known that the Americans wash the TNT with sulphite and bicarbonate of soda for the sole purpose of eliminating the bad odor which pervades the workrooms.

It is worth while noting here that the irritating odor of crude TNT is distinctly noticed during the washing of the product with hot water (carrying off by steam).

As to the danger of tetra-nitro-methane we do not believe it to be very marked, because, according to the French patent No. 384079, of November 16, 1907, Paul Winaud proposes the use of a mixture of tetra-nitro-methane and combustible bodies to replace panclastites (a mixture of liquified nitrous gases and combustible bodies), making a point of the fact that the tetra-nitro-methane is much less toxic than nitrous vapors.

The grinding of pure TNT does not irritate the eyes but does produce dust. The purification of TNT makes it lose both its odor and its greasy consistency.

St. Chamas, May 27, 1918.
The Military Technical Agent.
Signed: KOVACHE.

APPENDIX 4.

Note on the Elimination From Crude TNT of a Poisonous Product—Tetra-Nitro-Methane.

A number of fatal cases of intoxication have recently been observed in England among workers manipulating crude TNT.

Moreover, in an article appearing in a German review[1] on the toxicity of nitrogen derivatives, the accidents observed in the manufacture of TNT have been attributed principally to the action of tetra-nitro-methane of which the toxicity appears to be remarkable.

The elimination of this product from the crude TNT thus appears most desirable, and we have been led to find out how the tetra-nitro-methane behaves in the course of purification by sulphitization.

[1] Extraits des pĕriodiques Chimiques Allemands (Ministère de l'Armement, Fascicule VIII. P. 578.).

We have heretofore studied the solubility of this product and new experiments have confirmed our observations. Tetra-nitro-methane in contact, when cold, with a dilute solution of sulphite (4 to 5 per cent of anhydrous sulphite) dissolves with great rapidity and with an elevation of temperature. The reaction is much more energetic than that of asymetric TNT, and *it is certain that, in the course of the purification by sulphitization, the tetra-nitro-methane disappears very rapidly.* What is the mechanism of this reaction?

The most plausible hypothesis consists in admitting a reaction analogous to that of the sulphite of sodium on asymetric TNT, namely, the substitution of a sulphite group for a nitrite group.

By the reaction:

$$C(NO_2)_4+SO_3Na_2=C(NO_2)_3SO_3Na+NaNO_2$$

there is thus obtained tri-nitro-methane sulphite of sodium soluble in water.

In fact, the reaction is more complex, since the preceding equation implies a maintenance of neutrality, whereas the solution becomes acid very quickly and there is observed a release of nitrogen dioxide.

This phenomenon appears to us to be explained in the following manner:

As a first phase there is indeed formed tri-nitro-methane sulphite of sodium, but this unstable compound hydrolyzes quickly, according to the equation:

$$C\begin{cases}(NO_2)_3\\SO_3Na\end{cases}+H_2O=C\begin{cases}(NO_2)_3\\H\end{cases}+SO_4NaH$$

giving rise to tri-nitro-methane and sodium bisulphate.[1]

The reaction of these products on the sodium nitrite formed in the first reaction would give rise to nitrogen dioxide.

In order to confirm this hypothesis we have tried to identify the tri-nitro-methane formed.

The yellow solutions obtained present the characteristics of this body: Discoloration under the action of very concentrated acids and the passing over of the coloring body in the steam. To identify the tri-nitro-methane we have proceeded in the following manner:

Three cc. of tetra-nitro-methane are treated with a solution of 10 gr. of sodium sulphite in 100 cc. of water. The solution, of a strong yellow color, is acidified by H_2SO_4, then extracted with ether. The ether is treated with an excess of silver oxide to a neutral reaction; the ether solution is then decanted and evaporated.

[1] It is possible that this reaction may be due to an autocatalysis, the first traces of acid form favoring the hydrolysis of tri-nitro-methane sulphite. Perhaps the yellow solution obtained in carrying out the reaction of an ammoniacal solution of sulphite on tetro-nitro-methane may contain, unaltered, tri-nitro-methane sulphite of sodium. This point remains to be determined.

We have thus obtained the explosive silver salt of tri-nitro-methane described by Hantzoch and Hichenberger (Ber. 32 P. 636, 1899), a silver salt of which the solubility in ether may be considered as characteristic.

RÉSUMÉ.

1. Tetra-nitro-methane may easily be eliminated from crude TNT by the treatment of sulphitization.

2. The reaction seems to be carried out in two phases: (*a*) The formation of tri-nitro-methane sulphite of sodium, and (*b*) the hydrolysis of this product with the formation of sodium salt and tri-nitro-methane.

Paris, August 7, 1917.
Chief Chemical Engineer.
Signed: MURAOW.

Approved:
Chief Engineer in charge of the Service of Chemical Studies.
Signed: MARQUEYROL.

Approved:
Chief Engineer, assistant to the Director of the Service of I. E. E. T. P.
Signed: LIOUVILLE.

APPENDIX 5.

Note on the Vascular Effects of the Inhalation of the Vapors of Nitrated Toluene.

(Dr. MAYER.)

In a former note we have shown that when the products which leave the oils of toluene, maintained at 100° C., are carried off in steam, these products inhaled by an animal produce no vasomotor effects.

It is desirable to know if the vapors given off under the same conditions by mono-nitro-toluene (ortho- and para-) or by di-nitro-toluene 1–2–4 produce vasomotor effects.

We have made experiments to determine this question. A rabbit was tracheotomized. A canula was placed in the trachea and connected with a T-tube whose horizontal branch was traversed by an air current charged with the vapors given off when the nitrated toluenes were heated to 100° C. in a hot-water bath. The blood pressure and pulse were registered. The inhalation continued for about 15 minutes.

It can be seen from the attached curves that this inhalation produced no vascular effects.

NOTE.—The curves noted, which can not be readily reproduced, show that there is no change of blood pressure either at the beginning or the end of the experiment.

APPENDIX 6.

Note on the Toxic Effects of Oils of Xylene and Nitrated Toluene.

(Dr. MAYER.)

It is desirable to determine whether the commercial products which result from the nitration of the oils of xylene and toluene produce toxic effects. It is especially desired to know if they have an action analogous to that of nitroglycerin, which, when introduced into the organism, gives rise to widespread vaso-dilatations.

To determine this question we have been provided with the following samples:

1. Oil of trinitrated xylite; Marqueyrol process.
2. Oil of di-nitro-xylene coming from the drying out of crude xylite, sent by the powder works of St. Chamas.
3. Oil of di-nitro-toluene also sent by the powder works of St. Chamas.

I. GENERAL TOXICITY.

We have undertaken to determine the toxicity of these products by injecting them subcutaneously into dogs. To make possible this injection we have put these products into suspension in oil.

The results of our experiments are condensed in the following table:

Dose in grams per kilogram of animal.	Oil of di-nitro-toluene.		Oil of di-nitro-xylene.		Oil of xylite trinitrated.	
	Weight of dog.	Result.	Weight of dog.	Result.	Weight of dog.	Result.
	Kg.		*Kg.*		*Kg.*	
0.5	9.	Dead after 20 hours...	12	Dead after 24 hours...	12	Dead after 24 hours.
.2	10.5	Survived............	9	Survived............	21	Dead after 30 hours.
.1	15	.....do.............	14	.....do.............	32	Survived.
.1	....	....	....	....	15	Do.
.05	16.5	Survived............	14.5	Survived............	18	Do.

It is seen that the oil of di-nitro-toluene causes a fatal intoxication in doses of 0.50 gr. per kg.; the oil of di-nitro-xylene in doses of 0.50 gr. per kg.; and the oil of tri-nitro-xylene in doses of 0.20 gr. per kg. These products are thus relatively slightly toxic. The nitrated compounds of xylene and toluene appear to have the same order of toxicity.

II. LESIONS PRODUCED BY OILS OF XYLENE AND NITRATED TOLUENE.

The oils of xylene and nitrated toluene injected into animals produce toxic effects. These effects seem to react upon the principal vital organs, in particular upon the liver and kidneys.

We have studied, from a cytological point of view, the organs of animals which have succumbed after injections of the products experimented upon, and have made the following observations:

Oil of trinitrated xylite—(*a*) *Liver.*—As a whole the liver is congested. Cytologically it presents extremely definite lesions. These lesions consist in alterations of the chondriome of the type of homogenization. Almost all the areas examined in section show this homogenization in the second degree, and sometimes in the third degree. Moreover, there is noted in almost all the cells the presence of fine fatty granulations. The toxic processes thus concern the phosphatides of the liver.

(*b*) *Kidneys.*—The kidneys also present cytologic lesions; the Strands of Heidenheim have disappeared; the protoplasm is gathered together in masses in the form of a coarse network. This network holds granulations whose dimensions are sometimes considerable. The appearance of the chondriome is that of homogenization in the first and second degree.

Oil of dinitrotoluene and of dinitroxylene—(*a*) *Liver.*—The liver is congested and cytologically injured. Above all the chondriosome appears to be altered. The granulations are often indistinct. Furthermore the cells contain abnormal inclusions, which reduce osmic acid, and are soluble in the solvents for fatty bodies, thereafter leaving their trace in permanent slides in the form of round vacuoles.

(*b*) *Kidneys.*—The kidneys present slight cytological lesions; homogenization in the first degree.

These cytological observations are corroborated by chemical analysis of the tissues. The liver contains a large quantity of fixed fatty acids, and a quantity of insaponifiable substances much greater than normal (for 100 gr. dry: Fixed fatty acid, 10.89 gr.; cholesterine, 0.55 gr.; other insaponifiable substances, 2.46 gr.).

Thus the products examined, when administered in fatal doses, cause very important lesions of the liver and alterations of the kidneys.

III. THE ACTION ON BLOOD PRESSURE.

It is known that nitroglycerin (used in France under the trade name of trinitrine) is a strong vasodilatator. The vasodilatation which it produces is so extensive that the organism is not able to compensate for it, and the arterial pressure is markedly lower after administration of this product. This lowering of pressure is produced after intravenous injections in the rabbit in doses of about 0.003) gram per kilogram.

We have injected either under the skin or into the peritoneum (it has been impossible to make satisfactory injections into the veins) considerable doses of oils of xylene and of toluene. We can say im-

mediately that the effect obtained is in nowise comparable with that of nitroglycerin.

1. When these products are injected into the peritoneum there is indeed, at the moment of injection, a sharp falling of pressure. But this is to be ascribed to the puncture of the skin and the injection itself. This action can be reproduced by simple injection of oil. Shortly after the injection the pressure comes back to normal (fig. 2).

When these products are injected under the skin the fall of pressure is scarcely noticeable and is extremely brief.

2. When one follows the animal into which oils of xylene and toluene have been injected, he sees the pressure remount after injection and maintain itself for sometime at normal level. Then it lowers progressively during the time in which the intoxication progresses. There is no effect comparable to the sudden and transient action of nitroglycerin.

From a practical point of view the question comes up to determine whether the vapors given off by the oils tested may produce effects of vasodilatation.

We have undertaken to make vapors coming from these products penetrate into the respiratory tracts of the rabbit. The oil was kept boiling in a flask placed in a water bath. A current of air carried away the vapors whose odor was clearly perceptible. Next the vertical branch of a tracheal canula of T-shape was placed in the trachea of the animal and the current of air charged with vapors was sent through the horizontal branch. The rabbit thus breathed air containing the products to be experimented with.

Under these conditions we have not discovered any fall of arterial pressure in the subject under experimentation.

The oils studied do not thus emit vasodilating vapors.

CONCLUSIONS.

1. The oils of di-nitro-toluene and of di-nitro-xylene and the oils of trinitrated xylite are toxic. The fatal dose for the dog was for the first two, 0.50 gram per kg.; for the last one, 0.20 gram per kg.

2. They produce important lesions of the liver and kidneys.

3. They have no vasodilating effects analogous to those of nitroglycerine.

4. Their vapors, when inhaled, do not lead to a fall of arterial pressure.

NOTE.—The curves with the original show that while controls with tri-nitrine give a marked change in pressure, with the materials under experiment there are no such changes.

APPENDIX 7.

Note on the Toxicity of Several Commercial Nitrated Products of Benzene, Phenols, and Toluols.

(Dr. Mayer.)

We have attempted to establish the minimum fatal doses for several commercial nitrated products of benzene, phenols, anisols, and toluols.

1. *Chlorobenzene* coming from the liquid-air factory at Montereau.
2. *Mono-nitro-chlorobenzene* coming from Montereau.

(*a*) Intimate mixture of para and ortho mono-nitro-chlorobenzene, which solidifies at about 12° C. and separates by centrifugation.

(*b*) Para, perhaps containing a little of the ortho separated by being carried off by steam, and melting at about 80° C.

(*c*) Para mono-nitro-chlorobenzene, practically pure and melting at about 83° C.

3. *Para-di-chloro-nitrobenzene*, coming from Montereau.
4. *Di-nitro-chlorobenzene*, coming from Montereau, and forming, at ordinary temperatures, a mixture of oils and crystals.
5. *Di-nitro-di-chlorobenzene*, coming from Montereau.
6. *Commercial di-nitro-phenol 1.2.4*, coming from Montereau.
7. *Tri-nitro-phenol*, coming from the Gillet factory.
8. *Di-nitranisol 1.2.4*, coming from Montereau.
9. *Tri-nitranicol*, coming from Montereau.
10. *Di-nitro-toluol 1.2.4*, acquired at Poulenc.
11. *Di-nitro-toluol 1.2.6*, acquired at Poulenc.

All these bodies have been experimented upon in the following manner:

Solution in ether; mixture of the ether solution with olive oil; evaporation in electric sand bath; subcutaneous injection of the material in the oil. The experiments have been carried out on the dog. Under these conditions we have obtained the results shown in the following tables:

CHLORO-BENZENE.

Number of grams per kg. of animal.	Initial weight of the animal in kgs.	Fate of the animal.
1.0	16.7	Survived.

MONO-NITRO-CHLORO-BENZENES.

(1. Mono-nitro-chloro-benzine. Intimate mixture of para and ortho, solidifying at about 12° C., separated by centrifuging of the first.)

1.0	19	Dead after 1 day.
1.0	12	Do.
.5	12	Survived.
.5	19	Do.

MONO-NITRO-CHLORO-BENZENES—Continued.

(2. Mono-nitro-chloro-benzene. Para, perhaps containing a little ortho, separated by being carried off by steam.)

Number of grams per kg. of animal.	Initial weight of the animal in kgs.	Fate of the animal.
0.5	13.5	Dead after 2 days.
.25	9	Survived.

(3. Mono-nitro-chloro-benzene. Para, practically pure.)

0.5	9	Dead after 24 hours.
.5	10	Do.
.5	12	Survived.
.25	11	Dead after 5 days.

DI-NITRO-CHLORO-BENZENE.

1. OILY PART.

0.5	12	Dead after 1 day.
.5	12.2	Dead after 2 days.
.1	12	Survived.
.1	12.2	Do.

2. CRYSTALS.

0.3	25	Dead after 2 days.
.3	16.5	Survived.
.1	23	Do.
.1	16.5	Do.

PARA-DI-CHLORO-NITRO-BENZENE.

1.0	7	Died during the night.
.5	6	Dead after 48 hours.
.25	6	Survived.
.1	6	Do.

DI-NITRO-DI-CHLORO-BENZENE.

1.0	58	Died during the night.
.5	7	Do.
.25	8	Dead after 5 days.
.1	7	Survived.

DI-NITRO-TOLUOL.

1. DI-NITRO-TOLUOL 1-2-4.

0.5	6	Dead after 8 hours.
.2	8.5	Dead after 4 days.
.1	13.5	Survived.
.1	8.5	Do.
.05	13.5	Do.

DI-NITRO-TOLUOL—Continued.

2. DI-NITRO-TOLUOL 1-2-6.

Number of grams per kg. of animal.	Initial weight of the animal in kgs.	Fate of the animal.
0.1	14.50	Dead after 2 days.
.1	13	Dead after 8 days.
.05	13	Survived.

DI-NITRANISOL 1-2-4.

1.0	8	Died during the night.
.5	5	Do.
.1	6	Dead after 48 hours.
.05	7.5	Dead after 3 days.
.05	7	Survived.
.03	7	Do.
.03	9	Do.

TRI-NITRANISOL.

1.0	6	Dead after 48 hours.
.5	6	Do.
.1	8	Dead after 24 hours.
.05	10	Survived.
.05	9	Do.

TRI-NITRO-PHENOL 1-2-4-6.

0.5	4	Dead after 4 hours.
.1	22	Dead after 6 hours.
.05	13	Survived.
.05	22	Do.
.03	13.8	Do.
.03	13.6	Do.

DI-NITRO-PHENOL 1-2-4.

0.1	22.7	Dead after 1 hour.
.1	17	Do.
.05	20	Do.
.05	13.5	Dead after 1 hour and 30 minutes.
.03	22	Dead after 2½ hours.
.03	13	Dead after 3 hours.
.03	12	Survived.
.02	17.5	Do.
.02	17	Do.

We have condensed our results into a graph (see Chart 4) which indicates the minimum fatal dose either for 12 hours or for 10 days following the injection.

The inspection of this graph shows that certain bodies in the minimum fatal dose give rise to a superacute intoxication. Such bodies are di-nitro-phenol 1–2–4 and tri-nitro-phenol. Other bodies, on the contrary, when injected in limited doses, produce only a slow intoxication.

We may add that among these latter bodies certain of them are able, if injected in sufficiently strong doses, to lead rapidly to death, while others, even in strong doses (1 gram per kg.), do not produce death in 12 hours.

CONCLUSIONS.

1. The chloro and nitro-chloro-benzene are clearly less toxic than the nitro-toluol, anisols, and phenols.

2. For the commercial products which we have had in hand the doses leading to death in 12 hours are as follows:

	Gram per kg. of animal.
For the di-nitro-phenol 1–2–4	0.03
For the tri-nitro-phenol	.10
For the di-nitranisol	.50
For the di-nitro-toluol 1–2–4	.50
For the di-nitro-di-chloro-benzene	.50

The minimum doses leading to death are as follows:

	Gram per kg. of animal.
For the di-nitro-phenol 1–2–4	0.03
For the di-nitranisol 1–2–4	.05
For the tri-nitro-phenol	.10
For the tri-nitranisol	.10
For the di-nitro-toluol 1–2–6	.10
For the di-nitro-toluol 1–2–4	.20
For the di-nitro-di-chloro-benzene	.25
For the di-nitro-chloro-benzene	.50
For the para-di-chloro-nitro-benzene	.50
For the para-nitro-chloro-benzene	[1].75
For the mono-nitro-chloro-benzene	.50
For the chloro-benzene	[1]1.00

[1]About.